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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/618,178 | 07/18/2000 | Stephen E. Lincoln | 13020-10 | 9015 |

7590 12/18/2003

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| EXAMINER | |
|---|---|
| FREDMAN, JEFFREY NORMAN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/618,178 | LINCOLN ET AL. | |
| | Examiner | Art Unit | |
| | Jeffrey Fredman | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 February 2003* .

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *51-54 and 56-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-54 and 56-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Status*

Claims 51-54 and 56-105 are pending.

Claims 51-54 and 56-105 are rejected.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

### *Claim Rejections - 35 USC § 112 – second paragraph*

1. Claims 96-105 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is a "genotypic class identifier" as stated in claim 96. The specification does not use this term (as noted in the new matter rejection below). There is no definition of this term. It is unclear what limitations are imposed by the term "identifier" with regard to the genotypic class. It is further unclear how these identifiers are correlated with "confidence measures".

### *Claim Rejections - 35 USC § 112 – New Matter*

2. Claims 96-105 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

Here, claims 96-105 are composed of new matter. In particular, there is no support for the term "identifier" in the specification, nor is there any support for correlation of the "identifier" with a "confidence measure". A careful review by the examiner of the cited pages of the specification failed to identify any support for this new limitation.

Since no basis has been found to support the new claim limitation in the specification, these claims are rejected as incorporating new matter.

***Priority***

3. Applicant's claim of priority back to application 08/173,173, 07/775,786 and 07/664,837 is noted. The examiner was unable to determine whether these applications provide support for the entirety of the current claims and therefore the claims are given the effective date of the immediate parent 09/088,820, which provides express support (except for claim 50, as detailed below).

***Claim Rejections - 35 USC § 102***

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sal in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 51-54 and 69-74 are rejected under 35 U.S.C. 102(b) as being anticipated by Kimpton et al (PCR Meth. Appl. (August 1993) 3:13-22).

Kimpton teaches a method of determining the genotype at a locus within genetic material obtained by PCR amplification (page 14) comprising:

a) assembling reaction value data points for the samples, each reaction-value data point corresponding to a respective one of the samples and including at least one reaction value (here the data points represented by each of the separate peaks in figure 1 represents a different sample and are assembled in figure 2) (see pages 14-16),

b) determining an initial conditional probability for each reaction value data point for each genotype (here, the data was initially analyzed by analyzing the bands, to establish a conditional probability for reaction value (see page 15, subheading "statistical calculations and figure 1),

c) computing a conditional probability of each genotype for each reaction value data point (here, the calculation of band sizing determined the allele to which the sample belonged, thereby determining a genotype, since a genotype is composed of particular alleles at particular positions, see page 16, columns 2 and 3 and page 17, table 2)

d) determining the genotype and confidence score for each reaction value data point, thus determining the genotype and confidence score at the genetic locus for each sample (here, table 2 on page 17 provides for each reaction point the genotype and a standard deviation based on the data obtained from step d) (page 16 and page 17).

Kimpton expressly teaches reacting the material at multiple loci (page 14, table 1). On page 17, Kimpton expressly considers multiple alleles in the probability distributions, particularly in table 2 which expressly notes that the method is applicable to any number of alleles. Kimpton expressly teaches the use of multiple data points derived from multiple runs of the automated apparatus including multiple data sets in the exemplified method and apparatus (page 16, especially figure 2). Kimpton expressly teaches that the locus may be dinucleotide or tetranucleotide repeats (page 13). Kimpton expressly selected the loci for their discrimination ability and teaches that several different loci may be analyzed (page 16, column 1).

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 51-54 and 60-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton in view of Clark et al (Mol. Biol. Evol. (March 1990) 7(2):111-122).

Kimpton teaches the methods of claims 51-54 and 69-74 as discussed above. Kimpton does not teach modification of the data to iteratively improve the assay.

Clark teaches a method of resolving ambiguities by performing an iterative cascade of improvements on the data points (abstract and pages 111-113). Clark also applies the method to restriction site polymorphisms.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the iterative screening and improvement methods of Clark with the probability method of Kimpton since Clark states "Details of the algorithm for extracting allellic sequences are presented here, along with some population genetic considerations that influence the likelihood of success of the method. The algorithm also applies to the problem of inferring haplotype frequencies of closely linked restriction site polymorphisms (abstract)". An ordinary practitioner would have been motivated to apply the conceptual idea of iterative data processing of Clark in the genotyping method of Kimpton in order to extract the as close to the entirety of the allelic sequences as possible. Further, an ordinary practitioner would have recognized that the method could be performed using any length marker, including single nucleotide polymorphisms such as the restriction site polymorphisms expressly discussed and motivated by Clark.

6. Claims 51-54 and 56-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton in view of Clark et al (Mol. Biol. Evol. (March 1990) 7(2):111-122) and further in view of Goelet et al (WO 92/15712).

Kimpton in view of Clark teaches the methods of claims 51-54 and 60-74 as discussed above. Kimpton in view of Clark does not teach genetic bit analysis, which includes allele specific amplification.

Goelet teaches genetic bit analysis methods, including allele specific amplification methods (see entire document, expecially pages 10-13).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Kimpton in view of Clark with the use of genetic bit analysis or allele specific amplification to develop the data since Goelet states "The current invention provides a method that can be used to diagnose or characterize nucleic acids in biological samples without recourse to gel electrophoretic size separation of the nucleic acid species. This feature renders this process easily adaptable to automation and thus will permit the analysis of large numbers of samples at relatively low cost (page 8, lines 27-33)". An ordinary practitioner would have been motivated to substitute the equivalent genetic bit analysis method for PCR in order to minimize the need for gel electrophoresis and enhance the automatability of the process as expressly motivated by Goulet in order to speed analysis and minimize costs.

7. Claims 51-54, 56, 58 and 60-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton in view of Clark et al (Mol. Biol. Evol. (March 1990) 7(2):111-122) and further in view of Backman et al (U.S. Patent 5,516,663).

Kimpton in view of Clark teaches the methods of claims 51-54 and 60-74 as discussed above. Kimpton in view of Clark does not the use of ligation chain reaction.

Backman teaches a method of LCR (abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Kimpton in view of Clark with the use of LCR as taught by Backman since Backman states "One of the great strengths of amplification reactions is their ability to detect exceedingly small numbers of target molecules (column 2, lines 8-10)". An ordinary practitioner would have been motivated to substitute LCR for the equivalent amplification method of PCR for the express motivation that LCR can detect small numbers of target molecules and because LCR is a known equivalent amplification assay to the PCR used by Kimpton.

8. Claims 75-83, 85, 86, 88, 89, 91-93, 95, 96-99 and 103-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton et al (PCR Meth. Appl. (August 1993) 3:13-22) in view of Ledwina et al (Biometrics (1980) 36:161-165) and further as motivated in view of JeanPierre (Ann. Hum. Genet. (1992) 56:325-330).

Kimpton teaches a method of determining the genotype at a locus within genetic material obtained by PCR amplification (page 14) comprising:

a) Reacting the material at the locus to produce a first reaction value (see page 14, columns 1-3, subheading "Locus specific amplification conditions"),

b) forming a data set including the first reaction value by assembling reaction value data points for the samples, each reaction-value data point corresponding to a respective one of the samples and including at least one reaction value (here the data points represented by each of the separate peaks in figure 1 represents a different sample and are assembled in figure 2) (see pages 14-16),

e) determining the genotype and confidence score for each reaction value data point, thus determining the genotype and confidence score at the genetic locus for each sample (here, table 2 on page 17 provides for each reaction point the genotype and a standard deviation based on the data obtained from step d) (page 16 and page 17).

With regard to claim 77 and 78, Kimpton expressly teaches reacting the material at multiple loci (page 14, table 1). With regard to claims 80-82, on page 17, Kimpton expressly considers multiple alleles in the probability distributions, particularly in table 2 which expressly notes that the method is applicable to any number of alleles. Kimpton expressly teaches the use of multiple data points derived from multiple runs of the automated apparatus including multiple data sets in the exemplified method and apparatus (page 16, especially figure 2). Kimpton expressly teaches that the locus may be dinucleotide or tetranucleotide repeats (page 13). Kimpton expressly selected the loci for their discrimination ability and teaches that several different loci may be analyzed (page 16, column 1).

While Kimpton uses the Hardy-Weinberg test, Kimpton does not establish a distribution set of probability distributions and Kimpton does not then apply the reaction value of the distributions to detemine a measure of a conditional probability of each genotype of interest at the locus.

Ledwina teaches a method in which genotypes can be determined in which the Hardy Weinberg test is modified such that the steps of:

c) establishing a distribution set of probability distributions and associating hypothetical values with corresponding probabilities for each genotype of interest (see page 162 and page 163),

d) applying the first value to each pertinent probability distribution to determine a measure of conditional probability of each genotype of interest (see page 162 and page 163, especially "conditional distribution of T given Z=z" equation on page 163).

With regard to claim 76 and 79, Ledwina teaches a plurality of distributions which are hypothetical (see page 162, "common probability distribution of (T,Z) is multinomial with 1/2m(m+1) cells and with the vector of cell probabilities g=(g...).".

Further, JeanPierre motivates the use of computation of unknown genotypes to analyze the conditional probabilities relative to a distribution of hypothetical reaction values (see page 330).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Kimpton to use the conditional probability distribution method of Ledwina since Kimpton notes that the anlaysis uses the Hardy-Weinberg equilibria (see abstract) and since Ledwina states "The class of admissible tests for Hardy-Weinberg equilibrium in a multi allelic system is charactgerized. The standard goodness of fit chi square test is shown to be admissible for systems of two or more alleles. The conditional probability distribution required to determine the exact significance level of this test is presented (see abstract)". An ordinary practitioner would have been motivated to apply this hypothetical distribution analysis to genotyping since Jeanpierre notes the gains from creating such a

distribution include avoiding hazards such as incorrectly using the simple average of the conditional probabilities instead of the harmonic mean, to more accurately determine the genotype (see page 330).

9. Claims 75-86, 88, 89, 91-93, 96-99 and 103-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton et al (PCR Meth. Appl. (August 1993) 3:13-22) in view of Ledwina et al (Biometrics (1980) 36:161-165) and further as motivated in view of JeanPierre (Ann. Hum. Genet. (1992) 56:325-330).

Kimpton in view of Ledwina as motivated by JeanPierre teach the limitations of claims 75-83, 85, 86, 88, 89, 91-93 and 95 as discussed above. Kimpton in view of Ledwina as motivated by JeanPierre do not teach interation of the method.

Clark teaches a method of resolving ambiguities by performing an iterative cascade of improvements on the data points (abstract and pages 111-113). Clark also applies the method to restriction site polymorphisms.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the iterative screening and improvement methods of Clark with the probability method of Kimpton in view of Ledwina as motivated by JeanPierre since Clark states "Details of the algorithm for extracting allellic sequences are presented here, along with some population genetic considerations that influence the likelihood of success of the method. The algorithm also applies to the problem of inferring haplotype frequencies of closely linked restriction site polymorphisms (abstract)". An ordinary practitioner would have been motivated to apply the conceptual idea of iterative data processing of Clark in the genotyping method of Kimpton in view of Ledwina as motivated by JeanPierre in order to extract the as close to the entirety of the allelic sequences as possible. Further, an ordinary practitioner

would have recognized that the method could be performed using any length marker, including single nucleotide polymorphisms such as the restriction site polymorphisms expressly discussed and motivated by Clark.

10. Claims 75-83, 85-95, 96-101 and 103-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton et al (PCR Meth. Appl. (August 1993) 3:13-22) in view of Ledwina et al (Biometrics (1980) 36:161-165) and further as motivated in view of JeanPierre (Ann. Hum. Genet. (1992) 56:325-330).

Kimpton in view of Ledwina as motivated by JeanPierre teach the limitations of claims 75-83, 85, 86, 91-93 and 95 as discussed above. Kimpton in view of Ledwina as motivated by JeanPierre does not teach genetic bit analysis, which includes allele specific amplification, nor the particular alleles listed.

Goelet teaches genetic bit analysis methods, including allele specific amplification methods (see entire document, expecially pages 10-13). Goulet teaches single specific nucleotide alleles (see page 40, example 3). Goulet also shows a mutation which is associated, at least indirectly, with a restriction site (see figure 2).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Kimpton in view of Clark with the use of genetic bit analysis or allele specific amplification to develop the data since Goelet states "The current invention provides a method that can be used to diagnose or characterize nucleic acids in biological samples without recourse to gel electrophoretic size separation of the nucleic acid species. This feature renders this process easily adaptable to automation and thus will permit the analysis of large numbers of samples at relatively low cost (page 8, lines 27-33)". An ordinary practitioner would have been motivated to substitute the equivalent genetic bit analysis method for PCR in order to

minimize the need for gel electrophoresis and enhance the automatability of the process as expressly motivated by Goulet in order to speed analysis and minimize costs.

***Response to Arguments***

11. Applicant's arguments filed October 2, 2003, 2003 have been fully considered but they are not persuasive.

Applicant argues that the 102 rejection of claims 51-54 and 69-74 which relies upon the Kimpton reference is incorrect because Kimpton does not teach a distribution set of probability distributions. No such element is required by the rejected claims. Claim 72, for example, never refers to a distribution set of probability distributions. Therefore, it is noted that the features upon which applicant relies is not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is cited in the rejection itself. Further, the argument that Kimpton was satisfactory for it's purpose is not an argument that addresses the motivation. Every

reference states that it achieves the goals set out. If this argument was found persuasive, it would subvert the congressional intent in enacting section 103 of title 35, since every reference is complete in itself and no obviousness rejections would ever be made.

With regard to the new rejections including Ledwina, Applicant argues that the references are not combinable because the hypothetical person of ordinary skill would not have thought to combine these references. If this is an argument regarding motivation, specific motivation to combine is provided in the rejection. If this is an argument relating to the issue of analogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, all three references are in the same precise field of endeavor, that of genotypic analysis. In this very narrow field, each of the references is pertinent to the problem of analysis of genotypes.

12. Finally, the argument that it would "never have occurred to a hypothetical person" is not the standard for obviousness. The standard is set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). The inquiries that case imposed for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In the current case, the rejection analyses the claims using this framework. The content of the prior art is analyzed, with the differences between the claims and the prior art being specifically pointed out. There is no objective evidence of secondary considerations in this case for analysis and given the ordinary level of skill in this art, which is very high, the claimed invention is found obvious for the reasons given in the rejection.

Applicant reiterates that the "never have occurred" standard for each of the final rejections but this argument is not found persuasive.

***Conclusion***

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is currently 703-308-6568. In mid January, 2004, when TC 1600 relocates to the new USPTO facility in Alexandria, the examiner's phone number will become 571-272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The supervisor's new telephone number in mid January will be 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is currently 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634